Research Article

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The Efficacy of Magnesium Sulfate in Reduction of Post Cardiac Surgery Arrhythmia, Agitation and Pain: A randomized controlled study

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ABSTRACT

Background: *Arrhythmia, postoperative pain and agitation are a common complication after heart surgery and are a major source of morbidity and mortality.*

Aims: *This study aimed to study the efficacy of magnesium sulfate ($MgSO_4$) for reduction of post cardiac surgery arrhythmia, postoperative pain and agitation.*

Setting and Design: *This study design was a prospective randomized controlled double blinded clinical study.*

Patients and Methods: *140 adult patients that underwent elective cardiac surgery were randomized into 2 groups, Mg group (group magnesium), 70 patients received 30 $mg.kg^{-1}$ $MgSO_4$ in 500 cc normal saline and in group C (control group), 70 patients received 500 cc normal saline alone.*

Statistical Analysis used: *Mann-Whitney's, Chi square, Friedman's, factorial ANOVA, logistic and multiple regression analysis were used.*

Results: *Comparative study between the 2 groups revealed; significant decrease in arrhythmia events in Mg group; compared to control group; with significant statistical difference (p=0.023). The 2 groups showed marked decrease in VAS scores in Mg group; compared to control group; during the serial measurements. Comparative study between the 2 groups revealed non-significant difference as regards RASS score (p>0.05).*

Conclusion: *Mg significantly decreases the incidence of all type of postcardiac surgery arrhythmia and decrease the severity of postoperative pain and agitation.*

Keywords
Arrhythmia, Magnesium sulfate, Post cardiac, Agitation, Pain.

Introduction
Magnesium is an essential cation in the body and its homeostasis plays an important role in body's normal function. Magnesium ions are involved as a cofactor in more than 300 enzymatic reactions known in the body; they also participate in many processes such as hormones bind to receptors, calcium channel structure, and effective ion transfer of cell membrane, regulation of adenylate-cyclase, neuronal activity, vasomotor tone, heart muscle contraction, and release of neurotransmitters [1].

Inhibition of N-methyl D-aspartate receptors such as magnesium and receivers leads to a painful stimuli-induced inhibition of central sensitivity of the environment [2].

These effects mainly relate to controlling the entry of calcium into the cells by applying agonistic role on calcium receptors or antagonistic action on NMDA receptors [3].

After cardiac surgery, empirical magnesium sulfate has been studied extensively to reduce atrial fibrillation. Canadian Cardiovascular Society Guideline suggests prophylactic use of magnesium inpatients with contraindication to beta blocker and amiodarone for prevention of atrial fibrillation [4].

The advantage of magnesium sulfate is that it is a cheap drug with no known adverse effect other than systemic hypotension till date. In post-cardiac surgical setting with invasive arterial blood pressure monitoring, it is relatively easy to administer it as a slow infusion.

Patients and Methods

The study was approved by the department of anesthesia, faculty of medicine, Fayoum University and ethical scientific committees and obtaining an informed consent from the patients, This study is a prospective, randomized, single-blind, placebo controlled trial was performed in the cardiac operating room and ICU of El Fayoum University Hospital and in co-operation with National Heart Institute between December 2017, and July 2018.

Inclusion criteria included 140 Patients aged 18 -70- year old, both sexes, undergoing elective cardiac surgery with cardiopulmonary bypass (CPB) with an expected time of CPB between 45 minutes to 2 hours.

Exclusion criteria included Chronic AF, Heart rate <50, Prior history of AF, Previous history of cardiac surgery, Systolic blood pressure <100 mmHg, Recent MI (at previous 6 weeks), Current use of antiarrhythmic medication such as amiodarone, digoxin,Current use of warfarin, Patients with pacemaker, Atrioventricular (A-V) block, Ejection fraction <30%, Renal failure (creatinine >2.5 mg/dl), Pregnancy,Hepatic dysfunction (International Normalized Ratio >2, aminotransferases >100 IU), Current or history of neurological disease, History of drug addiction.

The patients were randomized into two groups (70 patient in each group) using computer-generated random number.

Magnesium sulfate group (Mg group)

70 patients were given 30 mg.kg^{-1} $MgSO_4$ in 500 cc of isotonic solution IV over 2 hrs after induction of anesthesia.

Control group (group c)

70 patients were given 500 cc normal saline solutions as placebo over 2 hrs after induction of anesthesia.

All patients were assessed one day before surgery all patients received similar premedication 1 mg oral lorazepam at night before surgery, 0.1 mg.kg^{-1} intramuscular morphine sulfate. Upon arrival to the pre-induction room, the patients received supplementary oxygen via a nasal cannula, and were monitored with ECG, NIBP and pulse oximeter. Under local infiltration anesthesia (lidocaine 2%), a peripheral venous cannula 16 G and a 20 G arterial cannula were inserted after Allen's test to select radial or ulnar arterial cannulation.

Anesthesia was induced in a slow, smooth, controlled fashion with thiopental 3-5 mg.kg^{-1}, fentanyl 2-10 µg.kg^{-1}, midazolam 0.1 mg.kg^{-1}, and pancuronium bromide 0.1 mg.kg^{-1}.

Patient was intubated with an oral cuffed endotracheal tube (ETT) size (7 to 7.5) for female and (8 to 8.5) for male, after confirming its position by capnograph and checked for the equality by stethoscope, it was connected to the ventilator with a minute volume of (6-10 ml.kg^{-1}.min^{-1}) and frequency 10-14.minute^{-1} to achieve a target alveolar partial carbon dioxide pressure between 35 and 40 mmHg and oxygen saturation not less than 94%.

After intubation a triple lumen central venous catheter triple-lumen 7.5 French central venous catheter (Amicath) was inserted in the right internal jugular vein and the bladder catheter was inserted to monitor urine output during and during the operation.

The nasopharyngeal temperature prop will be inserted to monitor the core temperature and the bladder catheter will be inserted to monitor urine output during and after the operation.

Anesthesia was maintained with isoflurane 0.5-1.5 minimum alveolar concentration (MAC) with incremental does of fentanyl 1-2 µg.kg^{-1} with total fentanyl does 25-35 µg.kg^{-1} and pancuronium 0.01 mg.kg^{-1} every 90minutes.

On cardiopulmonary bypass (CPB), anesthesia was maintained with propofol 50-100 µg.kg^{-1}.min^{-1}, incremental doses- if needed- of fentanyl and pancuronium.

Age, sexand weight was recorded preoperatively, Preoperative ECG, MAP, HR, and Oxygen saturation was recorded, Intraoperative ECG was recorded each hour from the start to the end of operation, Intraoperative MAP, HR, Oxygen saturation was recorded each hour from the start to the end of operation, Each 6 hours postoperative ECG was obtained and recorded, Postoperative assessment of pain according to Visual Analogue Scale pre-extubation, post-extubation and each 6 hours after extubation.

Postoperative assessment of the patient according to Richmond Agitation Sedation Score (RASS) figure 1 [5].

Score	Descriptor	Characteristics
+4	Combative	Combative, violent, immediate danger to staff
+3	Very agitated	Pulls or removes tube(s) or catheter(s); aggressive
+2	Agitated	Frequent nonpurposeful movement, fights ventilator
+1	Restless	Anxious, apprehensive but movements not aggressive or vigorous
0	Alert and calm	
-1	Drowsy	Not fully alert, but has sustained awakening to voice (eye opening and contact >10 seconds)
-2	Light sedation	Briefly awakens to voice (eye opening and contact <10 seconds)
-3		
-4	Moderate sedation	Movement or eye opening to voice (but no eye contact)
	Deep sedation	No response to voice, but movement or eye opening to physical stimulation
-5	Unarousable	No response to voice or physical stimulation

Figure 1: Richmond Agitation Sedation Score (RASS) [5].

Preoperative and postoperative magnesium level and Duration of ICU admission. The primary outcome of this study was the role of magnesium sulfate in reduction of post cardiac surgery arrhythmias and the secondary outcome was its role in controlling of postoperative pain and agitation.

Statistical Analysis

Data entry, processing and statistical analysis was carried out using MedCalc ver. 15.8. (MedCalc, Ostend, Belgium). Tests of significance (Mann-Whitney's, Chi square, Friedman's, factorial ANOVA, logistic and multiple regression analysis, and ROC Curve analysis) were used. Data were presented and suitable analysis was done according to the type of data (parametric and non-parametric) obtained for each variable. P-values less than 0.05 (5%) was considered to be statistically significant.

Mean, Standard deviation (± SD) and range for parametric numerical data, while Median and Inter-quartile range (IQR) for non-parametric numerical data, Frequency and percentage of non-numerical data.

Mann-Whitney's Test (U test) was used to assess the statistical significance of the difference of a non-parametric variable between two study groups, Friedman's test was used to assess the statistical significance of the difference of a non-parametric variable between more than two (paired) study group means, Repeated measures and factorial ANOVA tests was used to assess the statistical significance of the difference between more than two (paired) study group means; with the ability to insert grouping factors, which was used to generate clustered multiple variable graphs, Chi-Square test was used to examine the relationship between two qualitative variables.

Multiple linear regression: It was used to test and estimate the dependence of a quantitative variable based on its relationship with a set of independent variables, Logistic regression: useful in the prediction of the presence or absence of an outcome based on a set of independent variables. It is similar to a linear regression model but is suited when the dependent variable is qualitative (categorical). The ROC Curve (receiver operating characteristic) provides a useful way to evaluate the Sensitivity and specificity for quantitative Diagnostic measures that categorize cases into one of two groups.

Results

140 patients were included in our study and were randomly divided into two groups, and each group has 70 patients.

As regarding demographic data; Comparative study between the 2 groups revealed non-significant difference as regards age, weight and sex of the patients (p>0.05) table 1.

Variable		Control group (70)	Mg group (70)	P value
Age (years)		46 (36 – 53)	50 (40 – 59)	0.064
Weight (kg)		90 (85 – 95)	90 (85 – 97)	0.313
Gender	Female	25 (35.7%)	35 (50%)	0.124
	Male	45 (64.3%)	35 (50%)	

Table 1: Demographic data.
Mg group: Magnesium group; kg: Kilogram.

Comparative study between the 2 groups revealed non-significant difference as regards type of operations (p>0.05) table 2.

Variable		Control group (70)	Mg group (70)	P value
Type of operation	ASD	2 (2.9%)	0 (0%)	0.230
	CABG	30 (42.9%)	34 (48.6%)	
	CABG + VR	0 (0%)	2 (2.9%)	
	Fallot tetralogy	0 (0%)	1 (1.4%)	
	VR	38 (54.3%)	33 (47.1%)	

Table 2: Comparison between the 2 groups as regards type of operation.
Mg group: Magnesium Group. ASD: Atrial Septal Defect; CABG: Coronary Artery Bypass Grafting; VR: Valve Replacement.

Comparative study between the 2 groups revealed; significant decrease in arrhythmia events in Mg group; compared to control group; with significant statistical difference (p=0.023) (Table 3).

Comparative study between the 2 groups revealed non-significant difference as regards ICU admission days, RASS score and onset of arrhythmia (p>0.05) (Table 3).

Variable			Control group (70)	Mg group (70)	P value
Clinical outcomes	ICU admission (days)		3 (3 – 5)	3 (3 – 4)	0.207
	RASS score		0 (0 – 2)	0 (0 – 2)	0.072
ECG Outcomes	Normal		44 (62.9%)	57 (81.4%)	0.023*
	Arrhythmia (AF or other)		26 (37.1%)	13 (18.6%)	
	Onset of arrhythmia	Before CPB	5 (7.1%)	1 (1.4%)	0.210
		Rewarming	5 (7.1%)	0 (0%)	0.068
		Weaning	4 (5.7%)	3 (4.3%)	1.000
		Post CPB	2 (2.9%)	1 (1.4%)	1.000
		ICU admission	10 (14.5%)	8 (11.4%)	0.775

Table 3: Comparison between the 2 groups as regards outcome data.

The 2 groups showed marked decrease in VAS scores more in Mg group; compared to control group; during the serial measurements (Figure 2).

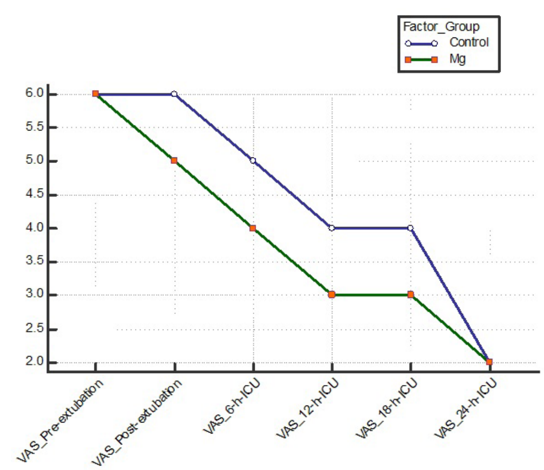

Figure 2: Comparison between the 2 groups of patients regarding serial VAS score assessments.

Discussion

The study was approved by the department of anesthesia, faculty of medicine, El-Fayoum University and ethical scientific committees and obtaining an informed consent from the patients, This study is a prospective, randomized, single-blind, placebo controlled trial was performed in the cardiac operating room and ICU of El-Fayoum University Hospital and in cooperation with National Heart Institute.

The primary outcome of this study was the role of magnesium sulfate in reduction of post cardiac surgery arrhythmias and the secondary outcome was its role in controlling of postoperative pain and agitation.

This study was conducted on 140 consecutive adult patients that underwent elective cardiac surgery. Patients were divided randomly into two groups; Magnesium sulfate group (Mg group), containing 70 patients given 30 $mg.kg^{-1}$ $MgSO_4$ in 500 cc of isotonic solution IV over 2 hrs after induction of anesthesia. On the other hand, the control group (group c), containing 70 patients given 500 cc normal saline solutions as placebo over 2 h after induction of anesthesia.

Regarding basic clinical, we found that; the mean age of all patients was (47.1 ± 11) years, and mean weight was (90 ± 9.8) kg. Regarding gender of the patients, the majority (57.1%) of patients were males; while (42.9%) were females.

Regarding pre-operative data, we found that; the mean baseline MAP, SO_2 and HR were (82.98 ± 11.51), (96.78 ± 2.71), (87.57 ± 10.2) respectively; and the average pH and Mg concentration were (7.39 ± 0.05), (1.7 ± 0.26) respectively. Regarding baseline ECG, nobody had arrhythmia.

Regarding type of operation, (1.4%) of patients had ASD operation, (45.7%) had CABG, (1.4%) had CABG and VR, (0.7%) had fallout tetralogy, (50.7%) had VR.

Regarding outcome data, we found that; the average duration of ICU admission and RASS score were (3.6 ± 1.04), (0.2 ± 0.48) respectively. Regarding cardiac outcomes, (27.9%) of patients had arrhythmia event (AF or other types); with (4.3%) of them happened before CPB, (3.6%) at rewarming, (5%) at weaning, (2.1%) of them happened after CPB, and most of them (12.9%) during ICU admission period.

Comparative studies regarding basic clinical and pre-operative data, revealed non-significant difference as regards age, weight and sex of the patients (p>0.05).

Comparative study between the 2 groups also revealed; highly significant decrease in baseline HR and pH in Mg group; compared to control group; with highly significant statistical difference (p<0.05 respectively).

Comparative study between the 2 groups also revealed; significant increase in baseline Mg concentration in Mg group; compared to control group; with highly significant statistical difference (p=0.029).

The previous results came in agreement with Naghipour and his colleagues in 2016, who reported that, there were no statistically significant differences regarding sex, age, hemodynamic and pre-operative parameters between two groups [6].

Comparative study between pre-extubation and post-extubation ICU measurements also revealed; highly significant decrease in VAS score measurements in Mg group; with highly significant difference (p<0.01).

Comparative study between pre-operative and post-operative measurements also revealed; highly significant increase in pH and Mg concentration measurements in Mg group; with highly significant difference (p<0.01 respectively).

We further analyzed and compared all 140 (paired) patients according to the serial measurements (pre, intra and post-operative); with entering a grouping factor (Mg or control); we found the following;

Serial comparative study between the 2 groups revealed; non-significant difference in repeated measurements of MAP, SO2 and pH (p>0.05 respectively).

The 2 groups showed marked decrease in HR in Mg group; compared to control group; during the serial measurements.

The 2 groups showed marked decrease in VAS scores in Mg group; compared to control group; during the serial measurements.

The 2 groups showed marked increase in Mg concentration in Mg group; compared to control group; during the serial measurements.

The previous results came in accordance with Peltoniemi et al [3], who reported that, the mechanism of analgesic effect of magnesium is not entirely clear; however, it seems interfering with calcium channels and NMDA receptors play an important role in this regard [3].

The findings of previous studies are largely consistent with our results although many studies have examined different doses of the drug.

In a study by Imani et al. [7], to assess the effects of magnesium sulfate on intrathecal analgesia after hysterectomy, it was found that magnesium sulfate led to longer duration of analgesia after surgery and reduced postoperative analgesic requirement [7].

Stomatology and Yan in [8], also studied the effects of magnesium sulfate on postoperative pain scores and extubation time in patients undergoing coronary artery bypass surgery. The results showed that extubation time was shorter in the group receiving magnesium than the placebo group. In addition, the average pain scores at 6, 12, 18, and 24 hours postoperatively in the group receiving magnesium sulfate were less than those of the placebo group were, and the need for morphine was also lower [8].

On the other hand, Shin et al. [9] studied the effects of intravenous magnesium sulfate removal on postoperative orthopedic pain. The first group received intravenous magnesium during surgery and the second group received the same dose of placebo. The group receiving magnesium had a lower pain scores at 1, 3, 6, and 12 hours compared to the control group. The amount of analgesic consumption within 24 hours in the group receiving magnesium was lower than that of the control group [9].

A decrease in pain and a reduction in opioid consumption after surgery significantly reduce the incidence of postoperative agitation caused by pain postoperative complications and increase patient satisfaction with surgery.

Comparative studies regarding cardiac outcomes revealed; significant decrease in arrhythmia events in Mg group; compared to control group; with significant statistical difference (p=0.023).

Comparative study between the 2 groups also revealed non-significant difference as regards ICU admission days, RASS score and onset of arrhythmia (p>0.05).

In this study, magnesium sulfate significantly decreased the incidence of arrhythmia in patients who underwent elective cardiac surgery compared with placebo.

Mohammadzadeh et al. [10], showed the prophylactic use of MgSO4 is effective at preventing arrhythmia that may occur following coronary bypass operations [10].

In addition, Lomivorotov et al. [11] concluded that the use of Mg in the preoperative and early postoperative periods is highly effective in reducing the incidence of AF after CABG [11].

Wu et al. [12], a meta-analysis study of 1251 patients reported that magnesium administration reduced the incidence of developing post-operative AF; however, it did not significantly decrease hospital length of stay or mortality [12].

De Oliveira et al. [13] conducted a meta-analysis that, suggested that magnesium had no effect on the incidence of post-operative stroke, myocardial infarction and death. Moreover, it mentions that magnesium did not decrease the hospital or intensive care unit lengths of stay. This study suggested that in higher quality studies MGS did not reduce post-operative supraventricular arrhythmias significantly [13].

Correlation studies between post-operative outcomes; and its relative independent predictors (baseline clinical, laboratory, ECG variables) revealed that; Multiple regression analysis shows that; after applying (Forward method) and entering some predictor variables; the increase in arrhythmia events; had an independent effect on increasing post-operative ICU stay; with significant statistical difference (p<0.01).

Multiple regression analysis shows that; after applying (Forward method) and entering some predictor variables; the increase in pre-operative baseline HR; had an independent effect on increasing post-operative RASS score; with significant statistical difference (p=0.023).

Logistic regression analysis shows that; after applying (Forward method) and entering some predictor variables; the decrease in (0-day) initial Mg concentration; had an independent effect on increasing the probability of arrhythmia occurrence; with significant statistical difference (p=0.0005).

ROC curve analysis to predict arrhythmia event for disease detection revealed that;

By using ROC-curve analysis, (0-day) Mg concentration at a cutoff point (≤1.7) discriminated patients with arrhythmia from patients without, with poor accuracy, sensitivity= 76% and specificity= 51% (p=0.0001).

By using ROC-curve analysis, baseline pH level showed non-significant predictive values in discrimination of patients with arrhythmia from patients without (p>0.05).

These results came in accordance with Kalita et al. [14], who stated that, the magnesium supplementation after cardiac surgery with cardiopulmonary bypass does favorably affect clinical outcomes [14].

This study had potential limitations as follows: first, the sample size of our study was limited that could adversely affect the power of the study; second due to possible influence of various factors on cardiac rhythm and amount of analgesia after surgery, third, the assessment of postoperative pain and agitation was done once during postoperative period.

We recommended further studies with a large number of patients, and evaluation of the effects of other factors such as type of surgical techniques

Conclusion

Mg sulfate significantly decreases the incidence of post cardiac surgery arrhythmia and decrease of postoperative pain and agitation at patients undergo cardiac surgery.

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